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Ischemic heart disease in patients with uremia undergoing maintenance hemodialysis

STEPHEN G. ROSTAND, JOHN C. GRETES, KATHARINE A. KIRK, EDWIN A. RUTSKY, and THOMAS E. ANDREOLI

Nephrology Research and Training Center, Department of Medicine and The Department of Biostatistics, University of Alabama Medical Center in Birmingham, and The Nephrology Section, Veterans Administration Hospital, Birmingham, Alabama

Ischemic heart disease in patients with uremia undergoing maintenance hemodialysis. The 6-year cumulative incidence of ischemic heart disease (IHD) in 382 dialysis patients (mean age [SEM], 43 ± 0.7 years) was studied. Of 101 patients with IHD, only 39 developed symptoms following dialysis (cumulative incidence, 20.8%). This group was older than those with IHD, and in 55%, IHD occurred in the first year of dialysis. Analysis by sex and race showed the rate of IHD in men and women to be similar, but the rate in whites was twice that in blacks. In men, the rate was not different from nondialysis men with similar coronary risk factors, whereas in dialysis women, the rate was twice that of a nondialysis cohort. The development of IHD did not adversely affect long-term survival in patients without prior evidence of IHD. Death from myocardial infarction occurred in 3 of 320 patients at risk. Autopsy data in 33 patients revealed 70% stenosis of coronary arteries in 7, 4 of whom had antecedent disease. Our major conclusions are *(a)* the incidence of IHD during dialysis was not different from similarly matched nondialysis subjects; *(b)* the rate of IHD in dialysis women was greater than it was in nondialysis subjects; *(c)* coronary artery disease only affected long-term survival of patients with preexisting disease; *(d)* autopsy data did not suggest accelerated atherosclerosis.

Maladie cardiaque ischémique chez les malades en hémodialyse chronique. L'incidence de la maladie cardiaque ischémique (IHD) a été étudiée chez 382 malades en hémodialyse dont l'âge moyen était de 43 ± [SEM] 7, sur 6 années cumulées. Parmi les 101 malades atteints d'IHD, seuls 39 ont eu des symptômes à la suite de la dialyse (incidence cumulée 20,8%). Ce groupe était plus âgé que celui indemne d'IHD et, pour 55% des malades, l'IHD est survenue au cours de la première année de la dialyse. L'analyse par sexe et ethnie a montré que la fréquence de l'IHD est la même chez l'homme et chez la femme, mais qu'elle est double chez les blancs par rapport aux noirs. Chez les hommes la fréquence n'est pas différente de celle observée chez les individus non dialysés ayant les mêmes facteurs de risque, alors que chez les femmes la fréquence est double de celle d'une population non dialysée. Le développement de l'IHD n'affecte pas péjorativement la survie à long terme des malades antérieurement indemnes d'IHD. La mort par infarctus du myocarde est survenue chez 3 des 320 malades exposés. Les constatations autopsiques chez 33 malades ont montré des sténoses coronariennes de 70% chez 7 d'entre eux, parmi lesquels 4 avaient une atteinte antérieure à la dialyse. Nos principales conclusions sont: *(a)* l'incidence de l'IHD au cours de la dialyse n'est pas différente de celle observée chez des sujets appariés non dialysés; *(b)* la fréquence de l'IHD chez les femmes dialysées est plus grande que chez les non dialysées; *(c)* la maladie coronarienne ne modifie la survie à long terme que si elle est pré-existante à la dialyse; *(d)* les constatations autopsiques ne suggèrent pas une accélération de la sclérose athéromateuse.

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It is widely accepted [1–7] that patients with end-stage renal disease have an accelerated rate of atherosclerosis and an accelerated mortality from coronary artery disease. But the data supporting this premise are few and derive largely from observations that show cardiovascular disease to be the most common cause of death in patients undergoing maintenance hemodialysis [1–7]. These studies, however, have not, in general, specified the type of cardiovascular disease in question and have not considered the fact that many dialysis patients with cardiovascular disease have identifiable heart disease prior to entering maintenance dialysis therapy. Lindner et al [4] have compared the incidence of *de novo* ischemic heart disease (IHD) in 39 patients on long-term hemodialysis to that of the Framingham study population [8]. Although they reported that their dialysis patients had an increased incidence of IHD and a greater mortality from IHD, the small size of their study population in contrast to the Framingham study group raises questions about the validity of such a comparison. Moreover, Lundin et al [9] have recently rebutted the concept that there is a greater incidence of heart disease in dialysis patients.

For these reasons, we evaluated the incidence of symptomatic IHD in a large dialysis population fol-

lowed up to 7 years at the Birmingham Veterans Hospital and at the University of Alabama Medical Center in Birmingham. We found that there were 39 new cases of IHD in 320 patients at risk between January of 1971 and January of 1978 and that more than half of these cases occurred in the first year of dialysis. The incidence of IHD was not significantly different from that found in the male population of a nondialysis cohort. In women, however, the rate of IHD was equal to that of men and was twice to three times greater than that for nondialysis subjects. During the 7-year period, only 3 of 320 patients died as a result of documented myocardial infarction.

Methods

We reviewed the records of 382 patients undergoing maintenance hemodialysis who had been followed for intervals up to 7 years (January of 1971 to January of 1978). The mean duration of this follow-up was 29.5 ± (SEM) 1.0 months. The patients selected for hemodialysis were from a cohort of 541 patients evaluated at the Birmingham VA Hospital and at the University of Alabama Medical Center in Birmingham between January of 1971 and December of 1975. During this time, few patients with diabetes mellitus were accepted for hemodialysis. Similarly, patients with disseminated cancer, with severe mental retardation, and with insurmountable socioeconomic problems were excluded. Some patients failed to return for further treatment following the initial diagnosis of end-stage renal disease and, hence, were followed no further. Patients with a past history of myocardial infarction or with angina pectoris, however, were not excluded from our program.

The mean age of this study population was 43.3 ± 0.7 years. The group was distributed nearly evenly between men and women (198 vs. 184) and between whites and blacks (196 vs 186). The population was divided into three groups. Group 1 included 62 patients with evidence of IHD prior to starting dialysis. Group 2 included 39 patients who developed symptomatic IHD following the onset of hemodialysis but who had no antecedent history of IHD. Group 3 included 281 patients who never exhibited symptoms of IHD either before or after hemodialysis. Table 1 presents the distribution of ages in the entire population under study and in each of the three subgroups.

Ischemic heart disease (IHD) was diagnosed when typical signs and symptoms of angina pectoris or myocardial infarction occurred. The diagnosis of myocardial infarction was confirmed by serial electrocardiographic (ECG) QRST changes, by enzyme changes, or, in certain instances, by autopsy. Routine fractionation of the enzyme creatine phosphokinase was available in our institution after 1975, and an MB fraction of greater than 10 U was considered diagnostic of myocardial injury. When a past history of myocardial infarction or angina pectoris prior to the onset of IHD was obtained and was documented in the patient's records, the patient was placed in group 1. The clinical, laboratory, and ECG criteria used to make the diagnosis of IHD are reviewed in detail by Logue and Hurst [10]. Left ventricular hypertrophy (LVH) was diagnosed by using the Estes electrocardiographic criteria [11]. Fasting plasma triglyceride concentrations were obtained during the first month of hemodialysis and were determined by standard laboratory techniques. Age-related normal values were similar to those described by Fredrickson, Levy, and Lees [12]. Initial blood pressure represents that pressure measured prior to the first hemodialysis. Information regarding the distribution and range of blood pressures in a randomly selected nondialysis group of Birmingham area residents was provided by Dr. Albert Oberman. Autopsies were performed on 33 of 132 patients who died during this study period. Histologic material was reexamined by Dr. Jack Geer of the Department of Pathology. Significant coronary occlusion was felt to be present when there was 70% or more narrowing of one or more major coronary vessels. Assignment of a cause of death was made from a review of the records of terminal hospitalizations and from death certificates.

Table 1. Age distribution of 382 patients undergoing maintenance hemodialysis

	Age, *years*					
IHD group	29	30 to 39	40 to 49	50 to 59	60	Total
Group 1	0	5 (7.8)	17 (17)	22 (25.3)	18 (33.9)	62 (16.2)
Group 2	2 (2.6)	7 (10.9)	13 (13.0)	14 (16.1)	3 (5.6)	39 (10.2)
Group 3	76 (97.4)	52 (81.3)	70 (70)	51 (58.6)	32 (60.5)	281 (73.6)
Total	*78*	*64*	*100*	*87*	*53*	*382*

[a] Values represent absolute number of patients in each age group. Numbers in parentheses represent the percentage distribution of each category by age group. Group 1 are patients with evidence of IHD prior to starting dialysis. Group 2 are 39 patients who developed symptomatic IHD following the onset of hemodialysis but who had no prior history of IHD. Group 3 include patients with no symptoms of IHD before or after hemodialysis.

The assignment of a cause of death was simplified somewhat because all patients were followed by us and because most deaths occurred in the hospital under our care.

Life-table methods were used to calculate both the cumulative survival of the dialysis patients and the cumulative incidence of IHD. The statistical analysis of these data was done with the Kaplan-Meier method for derivation of the cumulative incidence [13] and the Gehan's modified Wilcoxon test for doubly censored data for comparison of these curves [14]. Other statistical comparisons were made with three-way analysis of variances with covariance for age and with linear categorial model analysis [15]. Unless otherwise stated, all data are expressed as mean ± SEM.

Results

Risk factors for ischemic heart disease: (1) Age. Table 2 shows that the mean age for the group acquiring IHD (group 2) was significantly higher than that of the group without IHD, group 3 ($P = 0.009$) when adjusted for possible racial and sex differences. In the subset of patients between 40 and 59 years of age described in Table 3, no difference in ages was observed between the two IHD groups. There was, however, some evidence of a race-sex difference with respect to age, with white women being significantly older than white men ($P = 0.004$), whereas little age difference was present between the sexes in blacks.

(2) Blood pressure. Differences in systolic and diastolic blood pressure between groups 2 and 3 were investigated using three-way analysis of variance for race, sex, and IHD group effects, with covariance adjustment for age. Analysis of data in Table 2 reveals that for mean systolic blood pressure, there was no significant age adjustment. There was, however, a significant difference between the two racial groups. Blacks had a mean systolic pressure that was 17 mm Hg higher than that of whites ($P = 0.0006$). On the other hand, with respect to the diastolic blood pressure, age adjustment was highly significant ($P < 0.0001$). Both a significant sex dif-

Table 2. Coronary risk factors in patients without evidence of ischemic heart disease (IHD) and in those developing symptomatic IHD following onset of hemodialysis[a]

IHD status	Age *years*	Race, %		Initial systolic BP *mm Hg*	Initial diastolic BP *mm Hg*	Plasma triglyceride concentration *mg/dl*	LVH %
		Black	White				
Group 2	47.3 ± 1.6 (39)	38.5 (39)	61.5	173 ± 2 (32)	101 ± 4 (37)	160 ± 13 (34)	51.4 (37)
Group 3	40.5 ± 0.8 (281)	53.2 (281)	46.8	166 ± 2 (272)	99 ± 1 (272)	144 ± 5.2 (164)	43.8 (235)

[a] Values are mean ± SEM except for race and LVH which are percent. LVH is left ventricular hypertrophy. Numbers in parentheses represent sample size.

Table 3. Coronary risk factors in white and black dialysis patients aged 40 to 59 years[a]

Population at risk	Age *years*	Blood pressure[b] *mm Hg*		Plasma triglyceride concentration *mg/dl*	LVH %
		Initial systolic	Initial diastolic		
Black					
Men	49 ± 1 (25)	190 ± 8 (25)	114 ± 5 (25)	144 ± 18 (13)	66.7 (21)
Women	48 ± 0.7 (55)	177 ± 5 (53)	103 ± 3 (53)	134 ± 8 (39)	65.2 (46)
White					
Men	47 ± 0.8 (30)	164 ± 5 (30)	95 ± 3 (30)	169 ± 20 (15)	44.4 (27)
Women	51 ± 1.7 (38)	153 ± 4 (37)	85 ± 2 (37)	150 ± 12 (30)	31.4 (35

[a] Values represent mean ± SEM. Numbers in parentheses represent sample size. LVH is left ventricular hypertrophy.

[b] Mean systolic and diastolic blood pressures exceed 83% of the randomly obtained blood pressures of the white male population and 50% of those of the white female population in the Birmingham area ($N = 6433$). Mean systolic and diastolic blood pressures exceed 96% of the randomly obtained blood pressures of the black male and 86% of those of the black female population in the Birmingham area ($N = 3974$). (Data was supplied by Dr. A. Oberman.)

ference ($P = 0.04$) and a significant race by IHD group interaction were also present. Men had a mean diastolic blood pressure 5 mm Hg greater than did women. In the black population, group 2 had a significantly higher diastolic pressure than group 3. This difference was not noted among whites.

Analysis of the subset of patients between age 40 and 59 years (Table 3) revealed that the race difference in systolic blood pressure persisted ($P < 0.001$) but that the age adjustment remained insignificant. No other differences were significant. With respect to the mean diastolic blood pressure in this group of patients, however, the age adjustment was significant ($P = 0.01$), and both race and sex differences were also present. Blacks showed significantly increased diastolic pressures when compared to whites, and men exhibited higher diastolic pressures than women. Interestingly, the blood pressures in the white male patients were in the 83rd percentile of blood pressures obtained from randomly selected white men in the Birmingham area ($N = 2,798$), and those of white women subjects were in the 50th percentile of similarly selected white women of the same area ($N = 3,635$). Mean systolic and diastolic blood pressures of black men and women exceeded a 96th percentile of randomly selected black men ($N = 1698$) and the 86th percentile of a similarly selected group of black women in the Birmingham area ($N = 2276$).

(3) Plasma triglyceride concentration. A three-way analysis of variance coupled with an analysis of covariance for age was used to evaluate triglyceride differences between groups 2 and 3. In the data presented in Table 2, the age adjustment was not significant. There was, however, a significant three-way interaction for race, sex, and IHD ($P = 0.04$). The source of this effect appeared to be the white women, in whom the group acquiring IHD had the highest triglyceride concentrations whereas the group without IHD had the lowest. It is thought that this difference might be explained partially by differences in the disease processes causing renal failure in this group of women. We noted that women who did not acquire IHD had a high frequency of polycystic kidney disease as the precipitating cause of renal failure (18.2%). The analysis of triglyceride differences in the 40- to 59-year age group (Table 3) was conducted in the same manner. In this subset, neither the age adjustment nor any other effects were significant.

(4) Left ventricular hypertrophy (LVH). The differences in the prevalence of LVH among the race, sex, and IHD groups was investigated by using a linear categorical model approach, which allowed an age adjustment. The results of the analysis of the data in Table 2 showed that there was no significant age effect. Blacks, however, showed a significantly higher proportion of LVH than did whites ($P < 0.001$), and men had a significantly higher proportion of LVH than did women ($P = 0.02$). The IHD groups when adjusted for age, race, and sex were not significantly different with respect to the prevalence of LVH (Table 2). In the age group 40 to 59 years (Table 3), no significant age effect on LVH was noted. In this group, however, a significant interaction of race, sex, and IHD was noted ($P = 0.01$) and was caused by different patterns of LVH in the male population. Black men without IHD had more left ventricular hypertrophy than did those with IHD, whereas in the white males, the highest percentage of LVH was found in the group with IHD ($P = 0.01$).

(5) Incidence of ischemic heart disease (IHD). Of 382 dialysis patients in this study, 101 had IHD. Sixty-two were in group 1. Because that group had evidence of IHD preceding hemodialysis, it was excluded from any consideration of incidence. Thus, of 382 patients in the study, 320 were at risk for developing *de novo* IHD. During the observation period, 39 patients developed IHD for the first time, giving a 7-year incidence of 12.1% (Table 4). Of the 39 patients, 27 (69%) developed IHD by the end of the first year of hemodialysis. Table 4 also shows that the incidence of IHD in the overall population

Table 4. Incidence of ischemic heart disease (IHD) during 7 years of hemodialysis analyzed by age, race, and sex [a]

Population at risk	Women			Men			Total
	Black	White	Total	Black	White	Total	
Overall	11/96 (11.4)	14/69 (20.2)	25/165 (15.1)	4/68 (5.8)	10/87 (11.4)	14/155 (9.0)	39/320 (12.1)
40 to 50 years	7/55 (12.7)	9/38 (23.6)	16/93 (17.2)	3/25 (12.0)	8/30 (26.2)	11/55 (20)	27/148 (18.2)

[a] Numbers in parentheses represent percent of population. Denominators represent population at risk.

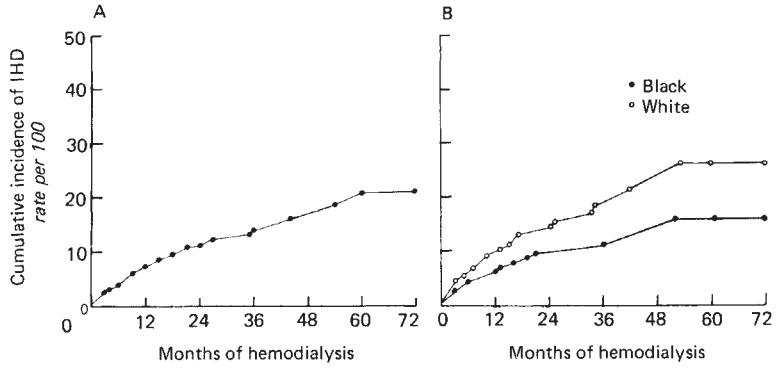

Fig. 1. A *Six-year cumulative incidence of ischemic heart disease (IHD) in 320 patients with negative histories of IHD prior to hemodialysis.* **B** *Six-year cumulative incidence of IHD in the white and black population at risk.* Open circles are whites (N = 155); closed circles are blacks (N = 165).

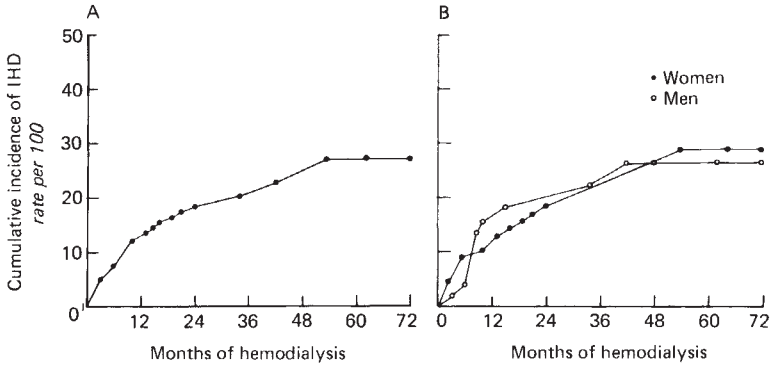

Fig. 2. A *Six-year cumulative incidence of ischemic heart disease (IHD) in 148 patients at risk (aged 40 to 59 years).* **B** *Six-year cumulative incidence of IHD in men and women aged 40 to 59 years.* Open circles are men (N = 55); closed circles are women (N = 93).

at risk was greater in women than it was in men (15.1 vs. 9.0%, $0.05 < P < 0.1$) and that the incidence in whites was nearly twice that in blacks (16 vs. 9%). Of 148 patients in age group 40 to 59 years, 27 (18.2%) developed IHD in 7 years. Again, the incidence of IHD in the first year of treatment was high, 16 of 27 patients (59.3%). The incidence of IHD in women in this group equaled that of men and IHD was also twice as frequent in whites than in blacks (25 vs. 12.5%). Because not all patients in this study were at risk for the same time, Life-table analysis was performed to determine the cumulative incidence of IHD. Figure 1A and the data in Appendix 1 reveal that for the entire population at risk, the cumulative incidence of IHD during 6 years of hemodialysis was 20.8%. The 6-year cumulative incidence of IHD in blacks (Fig. 1B) was 15.8%, whereas that of whites was 26.1% ($0.05 < P < 0.1$). Figure 2A shows the 6-year cumulative incidence of IHD in patients aged 40 to 59 years to be 26.9%. No significant difference in the rate of IHD could be seen between men and women, aged 40 to 59 years, after 6 years (26.2 vs. 28.6%, $P > 0.1$) (Fig. 2B).

Table 5 compares the incidence of IHD observed in the present study with that reported by Lindner et al [4] for the Seattle dialysis population and by

Table 5. Comparative incidence of ischemic heart disease in ages 40 to 59 years

Population	Rate per 100	
	Men	Women
Framingham[a]		
6-year incidence	22.6	8.5
Univ. of Alabama[b]		
6-year cumulative incidence	26.2	28.6
7-year incidence	20	17.2
Seattle		
6-year cumulative incidence (all ages)	26.4% (both sexes)	

[a] Abnormal in 2 or 3: hypertension, LVH, elevated plasma cholesterol

[b] Abnormal in 2 or 3: hypertension, LVH, elevated plasma triglyceride

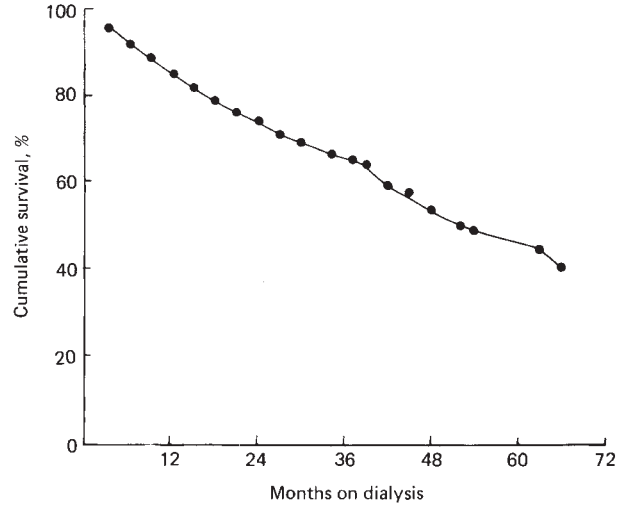

Fig. 3. *Cumulative survival of 382 hemodialysis patients.* Twelve months was 84.8%; 24 months, 74%; 36 months, 65%; 48 months, 53.3%; 60 months, 47.8%.

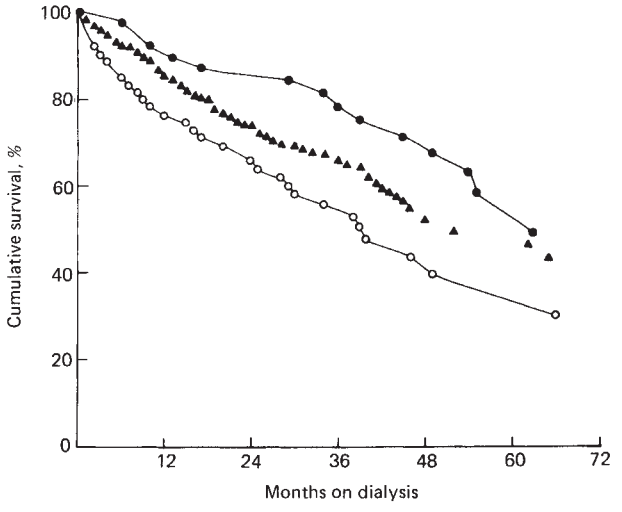

Fig. 4. *Effect of ischemic heart disease on cumulative survival of patients on maintenance hemodialysis. Open circles* represent patients with IHD prior to onset of hemodialysis ($N = 62$). *Closed circles* are patients developing IHD following onset of hemodialysis ($N = 39$). *Closed triangles* are patients exhibiting no symptoms of IHD ($N = 281$).

Kannel et al [8] for the Framingham population. It is apparent that the 6-year cumulative incidence seen in our cohort is similar to that of the Seattle cohort. Further, no difference in the incidence of IHD could be found between our male dialysis cohort and a nondialysis cohort of Framingham males (26.2 vs. 22.6%). Because the Framingham data represent a 6-year simple incidence, they were also compared with a simple 7-year incidence of IHD in our cohort. Once again, the data are similar for males. No matter how the data were analyzed, however, the incidence of IHD in female dialysis patients was greater than that seen for nondialysis women in the Framingham group (Table 5).

Effects of ischemic heart disease on patient survival. Figure 3 shows the cumulative survival for the 382 patients in this study. After 1 year of hemodialysis, 84.8% were alive; after 2 years, 74%; after 3 years, 65%; after 4 years, 53.3%; and after 5 years, 46.8%. Figure 4 shows that patients in group 1 had a significantly worse survival rate than those in group 3 ($P < 0.02$). Surprisingly, survival was significantly better ($P < 0.02$) in patients developing IHD after hemodialysis (group 2) in comparison with that of patients in group 3. Although not shown, the same relationship of IHD to survival was noted for the group of patients aged 40 to 59 years.

Causes of death and autopsy data. There were 132 deaths during the 7-year study period, and the distribution of the causes of death is listed in Table 6. Cardiovascular disease was the cause of death in 40 patients (30.3%). Of these, only 13 deaths were attributable to myocardial infarction. Pericarditis accounted for 7, stroke for 7, cardiomyopathy for 2, and arrhythmia for 5. Thus, the number of patients dying from documented myocardial infarction (13 or 9.8%) was not greater than those of our patients dying from pulmonary disease (16 or 12.1%) or from dialysis dementia (11 or 8.3%). Furthermore, of the

Table 6. Causes of death in the hemodialysis population of the University of Alabama Medical Center

Cause	Number	Percent
Unknown etiology	19	14.4
Cardiovascular	40	30.3
Stroke	13	
Myocardial infarction	13	
Pericarditis	7	
Tamponade	5	
Arrythmia	2	
Cardiomyopathy	2	
Arrythmia	5	
Dialysis dementia	11	8.3
Discontinued dialysis	16	12.1
Pulmonary disease	16	12.1
Pneumonia	1	
Edema	6	
Embolism	6	
Fibrosis	2	
Carcinoma	1	
Sepsis	11	8.3
Miscellaneous[a]	19	14.4
Total	*132*	*100*

[a] These include: exsanguination (3); hyperkalemia (8); starvation (5); hypoglycemia-lactic acidosis (1); trauma (1); breast-carcinoma (1).

patients dying of myocardial infarction, 10 patients had evidence of IHD prior to the start of hemodialysis. Hence, of 320 patients at risk, only 3 (1%) died of documented myocardial infarction during a 7-year period. Of interest was the finding that at autopsy one of the patients had infective endocarditis and had evidence of myocardial infarction due to vegetative emboli rather than to atherosclerosis (Table 7, patient 15). In 19 patients (14.4%), the cause of death was uncertain. Of this group, 10 patients had evidence of IHD prior to the onset of hemodialysis. Autopsy material was available for 33 of 132 patients dying in this study period (Table 7). Coronary artery narrowing of 70% or more could be found in only 7 patients. In 3 patients (patients 9, 20, and 23), IHD preceded dialysis and in a fourth (patient 16), dialysis duration did not exceed 3 months, making it difficult to attribute coronary artery disease to prolonged survival with renal failure. Severe aortic atherosclerosis could be found in only 11 patients, of whom only 2 were under age 40.

Discussion

Cardiovascular disease has been found to account for about 30% of deaths in patients with end-stage renal disease [1–3, 5]. This observation, coupled with the well-established finding of hypertension and hypertriglyceridemia in patients with end-stage renal disease [16–19] and the recent observation of a 20% 6-year cumulative probability of death from coronary artery disease reported by Lindner et al [4], has led to the view that atherosclerosis is accelerated in patients with end-stage renal disease and that IHD is a major mortality risk in patients undergoing maintenance hemodialysis. Our analysis of 320 patients at risk for IHD in the present study revealed that, in general, this group was hypertensive, had an elevated plasma triglyceride concentration, and had a greater than 40% incidence of LVH (Tables 2 and 3). Although these patients had an increased number of coronary risk factors, our data do not substantiate the view that IHD poses a significant mortality risk in all dialysis patients. Of 132 patients in this study who died, only 13 (9.8%) died of myocardial infarction. Further, 10 of the 13 had evidence of symptomatic IHD well before the initiation of maintenance hemodialysis. Thus, only 3 patients dying with documented myocardial infarction had no history of antecedent IHD. Stated in another way, only 1% of the 320 patients at risk for developing *de novo* IHD died of myocardial infarction.

These data are in accord with observations of Roguska et al [20] who found only three deaths from myocardial infarction in 131 patients undergoing dialysis between 1963 and 1972. Moreover, we found that the development of IHD during the course of hemodialysis did not affect adversely the survival of patients with a negative history of IHD prior to starting dialysis (Fig. 4). In fact, their survival rate was significantly better than that of patients who had not manifested findings of IHD. On the other hand, we found the survival of patients with evidence of IHD prior to the onset of hemodialysis was significantly worse in accordance with the observation of others [21]. Thus, we conclude that death from myocardial infarction was not a major risk in patients who exhibited no evidence of IHD before the onset of hemodialysis therapy.[1]

The 6-year cumulative incidence of IHD in our dialysis population at risk was 20.8%. Despite the fact that this group was ten times larger than the Seattle group reported by Lindner et al [4], the rates of IHD in both groups were similar (20.8 vs. 26.4%). Between 60 and 70% of our patients who developed IHD following the onset of hemodialysis did so before the completion of the first year of hemodialysis, which does not necessarily suggest that the atherosclerotic process had been accelerated, but rather that already existent, but asymptomatic, coronary artery disease may have been unmasked by the hemodynamically stressful hemodialysis procedure. If our view is correct, nearly half the new episodes of IHD seen following the onset of hemodialysis might in actuality represent preexistent disease, and thus perhaps the differences reported here and by others [4] between the incidence of IHD in patients with end-stage renal disease and in nondialysis subjects might well be reduced.

We realize that the systemic effects of uremia, and the use of hemodialysis with its attendant hemodynamic effects, in part, may make it difficult to find a truly matched nondialysis population to serve as a basis for comparison. Moreover, in the absence of data regarding smoking and body habitus, we are unable to evaluate the relative influence of these factors in the dialysis and nondialysis populations. Although we recognize these limitations, and that there are differences between the racial distribution in our group and the Framingham population, we

[1] Between 1971 and 1978, only one patient with symptomatic IHD underwent coronary artery bypass. Thus, in this study, the natural history of IHD was not altered by surgical intervention.

Table 7. Correlation of clinical and postmortem findings of ischemic heart disease (IHD) in 33 patients who underwent maintenance hemodialysis

Patient	Age, race, sex	Duration of dialysis *months*	IHD status	Cause of death[a]	Cause of renal failure[b]	Atherosclerosis aorta[c]	Coronary artery atherosclerosis ≥ 70% narrowing[d] RCA	LAD	LCA	Comments
1	55 WF	36	Group 2	Subdural hematoma	CGN	++	0	0	0	Metastatic myocardial calcifications
2	44 WF	10	Group 1	Pulm. embolus	Unk	+	0	0	0	
3	40 BF	11	Group 3	Pericardial tamponade	Unk	+	0	0	0	60% occlusion AV nodal artery; calcification AV node
4	64 WM	11	Group 3	Dialysis dementia	Unk	+	0	0	0	No coronary artery pathology
5	42 BM	3	Group 3	Pulm. edema	Unk	+	0	0	0	No coronary artery pathology
6	47 BF	7	Group 3	Sepsis	CGN	+	0	0	0	No coronary artery pathology
7	36 BM	23	Group 3	Pericardial tamponade	CGN	+	0	0	0	
8	52 BM	4	Group 3	D.C. dialysis	HBP	+	0	0	0	AV and SA nodes normal
9	59 BF	3	Group 1	Arrythmia	CIN	+	+	0	+	
10	17 WM	28	Group 3	Hypoglycemia-lactic acidosis	CGN	±	0	0	0	
11	50 BF	24	Group 1	Stroke	Unk	+	0	0	0	Minimal muscular hyperplasia of small coronary arteries
12	59 BF	17	Group 3	Hypokalemia	Amyloidosis	++	0	0	0	Amyloidosis of coronary vessels and L. atrial endocardium
13	52 WF	8	Group 3	Pneumonia	Polycystic	+	0	0	0	
14	52 WF	16	Group 3	Pulm. edema	HBP	+	0	0	0	Aspergillosis of myocardium
15	36 BM	45	Group 2	MI, SBE	HBP	++	+	+	+	Recent MI; calcified microemboli small coronary vessels. No chest pain until MI.
16	58 BF	2	Group 3	Arrythmia	CGN	+	0	+	0	Severe arteriosclerotic iliac & cerebral vessels
17	65 WF	21	Group 3	Dialysis dementia	Vasculitis	±	0	0	0	
18	17 WF	5	Group 3	HBP	Postpartum necrosis	±	0	0	0	
19	30 WM	13	Group 3	D.C. dialysis	HBP	±	0	0	0	Focal myocardial calcification
20	76 WM	2	Group 1	Pulm. fibrosis	CGN	+	+	+	+	Focal myocardial calcification; old scattered miliary infarcts
21	44 WF	9	Group 2	Dialysis dementia	Unk	++	0	0	0	
22	59 WF	6	Group 3	Dialysis dementia	CGN	+	0	0	0	
23	55 WM	20	Group 1	MI	Cortical necrosis	++	0	+	0	Old MI; fresh infarcts. AV and SA nodal arteries normal
24	65WF	29	Group 2	Dialysis dementia	CGN	+	0	0	0	Fibrosis of papillary muscles
25	50 BM	51	Group 3	Pulm. embolus	CGN	+	0	0	0	Calcific aortic valvulitis; coronary ostia patent patchy myocardial fibrosis
26	54 WM	12	Group 3	Arrythmia	Diabetes mellitus	++	+	+	+	Myocarditis; pericarditis
27	64 WF	68	Group 3	Sudden death	CIN	±	0	0	0	Myocardial fibrosis, mild
28	44 BM	42	Group 3	Arrythmia	HBP	++	0	0	0	Moderate myocardial fibrosis
29	45 WM	48	Group 3	Arrythmia	CGN	±	0	0	0	Extensive subendocardial calcification near AV node
30	35 WF	25	Group 3	Sepsis	Diabetes mellitus	++	0	0	0	Minimal calcification LAD
31	56 WM	34	Group 2	MI, Tbc	HBP	++	0	+	0	Extensive MI; caseating granulomas in myocardium, no chest pain until MI
32	66 BM	27	Group 3	Broncho-pneumonia	Unk	++	0	0	0	
33	56 BM	30	Group 3	Sepsis	HBP	±	0	0	0	Necrosis & calcification of mitral valve ring; multiple calcific microemboli.

[a] D.C. dialysis is discontinued dialysis; MI, myocardial infarction; SBE, subacute bacterial endocarditis; Tbc, tuberculosis.
[b] CGN = chronic glomerulonephritis; HBP = hypertension; CIN = chronic intersitial nephritis.
[c] Mild is ±; moderate, +; severe, ++.
[d] RCA = right coronary artery; LAD = left anterior descending artery; LCA = left circumflex artery.

have chosen, as did Lindner [4], to compare our results to the Framingham study, because the completeness of this study provides the most reasonable comparison. It should be noted that our patients had two or three of the following important coronary risk factors, hypertension, LVH, or hypertriglyceridemia, whereas those subjects in the Framingham study to whom we compared our patients differed in that plasma cholesterol was used as an index of plasma lipid concentration. In this regard, studies by Carlson and Bottiger [22] and Brown, Kinch, and Doyle [23] have shown that a parallel relationship exists for the prevalence of IHD and either plasma triglyceride or serum cholesterol concentration. Gotto et al [24] recently have shown a direct relationship between either plasma triglyceride or plasma cholesterol concentration and the severity of coronary artery disease. Thus, although we argue that the basis for our comparison is reasonable, we recognize the possibility that our results might have been different had measurements of cholesterol been made.

In our study, no difference was noted among men when either simple incidence or cumulative incidence of IHD was compared (Table 5). On the other hand, no matter what the basis of comparison, women with end-stage renal disease had a two- to three-fold greater incidence of IHD when compared to women in the Framingham study (Tables 4 and 5, Fig. 2B). Moreover, irrespective of race, the male predominance of IHD usually seen in the general population was not observed in the dialysis population. This is noteworthy because data from the Framingham study have shown that rates of IHD in women did not reach those of men until age 68 years [25]. It would appear from these data that the incidence of IHD in women with end-stage renal disease was increased.

It is not clear why the incidence of IHD in women was accelerated. Although the white women were significantly older than white men (Table 3), there was no difference in the ages of white men and women who developed IHD. The mean age for both groups was 47 years. No differences could be found between the ages of black men or women (Table 3). Moreover, the blood pressure and prevalence of LVH in women were lower than in men (Tables 2 and 3). Measurements of ponderal indices and smoking habits were not obtained, and thus their influence on the differing rates of IHD seen in men and women cannot be measured. Analysis of plasma triglyceride concentration, however, revealed that white women acquiring IHD had the highest triglyceride concentrations. Although it would be tempting to speculate on the reasons for the increased incidence of IHD in women, and to consider the effects of renal-failure-induced gonadal hormone abnormalities on this process, the data in our study do not allow us to address this question further.

The incidence of IHD was consistently greater in whites than in blacks (Fig. 1B, Table 4). This observation seemed surprising because blacks had significantly higher blood pressures and significantly more LVH than did whites. Again, we are unable to analyze the potential effects of smoking and body habitus on these differences. Nevertheless, the finding is in accord with several epidemiologic analyses of IHD in nondialysis populations that reveal the prevalence of IHD in blacks to be less than that of whites [26–27]. Thus, unlike the changes in the sex distribution of IHD disease seen in our dialysis population, no such changes were noted in its racial distribution.

Coronary artery lumenal narrowing of 70% or more was found at autopsy in only 7 of 33 patients dialyzed for 2 to 68 months (Table 7). In 3 patients, IHD preceded hemodialysis, and in a fourth, the short duration of dialysis (less than 3 months) suggested that the IHD may also have preceded hemodialysis. Similarly, severe aortic atherosclerosis was found in only 11 of the 33 patients who underwent autopsy. Only 2 of these patients were under 40 years of age. Our autopsy data, although limited, do not support the concept that atherosclerosis is accelerated in patients undergoing chronic hemodialysis.

Summary. We conclude that the incidence of IHD in men undergoing hemodialysis for end-stage renal disease is not greater than that seen in a nondialysis population of men with similar risk factors. In contrast, we have found the rate of IHD in women with end-stage renal disease to be accelerated when compared to similar nondialysis subjects. Our data also suggest that during the 7 years of hemodialysis IHD does not represent a major mortality risk in patients who have not had symptoms of IHD prior to hemodialysis, although it does pose a significant mortality risk in patients with evidence of established coronary artery disease prior to the onset of dialysis.

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Appendix

Appendix 1. Probability of developing ischemic heart disease (IHD) during hemodialysis[a]

Months of dialysis[b]	No. of patients entering[c]	Censored	No. developing IHD	Probability of developing IHD	Exact SEM
0	320	0	4	0.0125	0.0062
1	316	7	1	0.0156	0.0069
2	308	6	4	0.0284	0.0093
3	298	9	2	0.0349	0.0103
4	287	15	1	0.0383	0.0108
5	271	6	2	0.0454	0.0118
6	263	5	1	0.0490	0.0123
7	257	2	3	0.0601	0.0137
8	252	6	1	0.0639	0.0142
10	239	3	2	0.0716	0.0151
12	224	3	1	0.0757	0.0156
13	220	5	2	0.0841	0.0165
15	209	3	1	0.0885	0.0170
16	205	3	1	0.0930	0.0175
17	201	4	2	0.1020	0.0185
19	192	5	1	0.1067	0.0189
21	181	4	1	0.1116	0.0195
24	170	1	1	0.1168	0.0200
25	168	5	1	0.1221	0.0206
33	120	2	1	0.1294	0.0217
34	117	7	1	0.1369	0.0227
36	103	6	1	0.1452	0.0240
42	63	3	1	0.1588	0.0272
52	36	3	1	0.1822	0.0351
53	32	2	1	0.2077	0.0423
81	3	0	1	0.4718	0.2177

[a] Statistical analysis was by method of Kaplan and Meier [13].
[b] Entries are recorded only when an event (new episode of IHD) occurred.
[c] Last patient exited study at 84 months.

Appendix 2. Probability of developing ischemic heart disease (IHD) during hemodialysis: age, 40 to 59 years

Months of dialysis	No. of patients entering[a]	Censored	No. developing IHD	Probability of developing IHD	Exact SEM
0	148	1	2	0.0135	0.0095
1	145	3	1	0.0203	0.0116
2	141	4	3	0.0411	0.0164
3	134	5	1	0.0483	0.0178
5	125	1	2	0.0635	0.0205
6	122	2	1	0.0712	0.0217
7	119	0	3	0.0946	0.0250
8	116	3	1	0.1024	0.0260
10	111	0	2	0.1186	0.0279
13	103	2	2	0.1357	0.0299
15	98	0	1	0.1445	0.0308
16	97	1	1	0.1533	0.0318
19	92	1	1	0.1625	0.0327
21	87	2	1	0.1721	0.0337
24	79	1	1	0.1826	0.0349
34	53	1	1	0.1980	0.0375
42	30	1	1	0.2248	0.0448
53	18	1	1	0.2678	0.0595
81	2	0	1	0.6339	0.2613

[a] Last patient exited study at 84 months.

Appendix 3. Probability of developing ischemic heart disease (IHD) during hemodialysis: Black population

Months of dialysis	No. of patients entering[a]	Censored	No. developing IHD	Probability of developing IHD	Exact SEM
0	165	0	1	0.0060	0.0060
2	159	5	2	0.0185	0.0106
3	152	6	1	0.0250	0.0123
4	145	5	1	0.0317	0.0139
5	139	4	1	0.0387	0.0155
6	134	3	1	0.0458	0.0169
7	130	0	1	0.0532	0.0183
12	120	1	1	0.0611	0.0198
13	118	1	1	0.0690	0.0212
16	112	0	1	0.0773	0.0225
19	105	2	1	0.0861	0.0240
21	97	1	1	0.0955	0.0255
36	60	5	1	0.1106	0.0292
52	19	2	1	0.1574	0.0533

[a] Last patient exited study at 77 months.

Appendix 4. Probability of developing ischemic heart disease (IHD) during hemodialysis: White population

Months of dialysis	No. of patients entering[a]	Censored	No. developing IHD	Probability of developing IHD	Exact SEM
0	155	1	3	0.0193	0.0110
1	151	2	1	0.0258	0.0127
2	148	1	2	0.0390	0.0156
3	145	3	1	0.0456	0.0168
5	131	2	1	0.0529	0.0182
7	126	2	2	0.0679	0.0208
8	122	4	1	0.0756	0.0220
10	114	2	2	0.0918	0.0244
13	101	4	1	0.1008	0.0257
15	95	2	1	0.1102	0.0271
17	89	1	2	0.1302	0.0300
24	79	1	1	0.1412	0.0316
25	77	2	1	0.1524	0.0331
33	53	1	1	0.1684	0.0361
34	51	3	1	0.1847	0.0389
42	31	1	1	0.2110	0.0457
53	16	1	1	0.2603	0.0642
81	3	0	1	0.5068	0.2065

[a] Last patient exited study at 84 months.

Appendix 5. Probability of developing ischemic heart disease (IHD) during hemodialysis: Women, age 40 to 59 years

Months of dialysis	No. of patients entering[a]	Censored	No. developing IHD	Probability of developing IHD	Exact SEM
0	93	1	2	0.0215	0.0150
1	90	1	1	0.0323	0.0183
2	88	4	3	0.0653	0.0258
5	80	1	2	0.0887	0.0299
10	74	0	1	0.1010	0.0320
13	70	1	2	0.1267	0.0358
16	66	1	1	0.1399	0.0377
19	63	1	1	0.1536	0.0395
21	59	2	1	0.1679	0.0413
24	53	0	1	0.1836	0.0434
53	8	1	1	0.2857	0.1028

[a] Last patient exited study at 84 months.

Appendix 6. Probability of developing ischemic heart disease (IHD) during hemodialysis: Men, age 40 to 59 years

Months of dialysis	No. of patients entering	Censored	No. developing IHD	Probability of developing IHD	Exact SEM
0	55	2	0	0.0000	0.00
3	53	4	1	0.0188	0.01868
6	45	2	1	0.0406	0.0282
7	42	0	3	0.1091	0.0462
8	39	1	1	0.1320	0.0504
10	37	0	1	0.1554	0.0542
15	32	0	1	0.1818	0.0586
34	21	0	1	0.2208	0.0676
42	19	1	1	0.2618	0.0755
81	1	0	1	1.000	0.0000

Reprint requests to Dr. S. G. Rostand, Division of Nephrology, Department of Medicine, University of Alabama Medical Center, Birmingham, Alabama 35294, USA

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